Attorney's Docket No.: 07333-043001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Hartounian et al.
Serial No. : 09/192,064
Filed : September 10, 2001
Title : PRODUCTION OF MULTIVESICULAR LIPOSOMES

Art Unit : 1641
Examiner : Gollamudi Kishore, Ph.D.

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Commissioner for Patents
Washington, D.C. 20231

RESPONSE TO OFFICE ACTION MAILED NOVEMBER 28, 2001

Claims 1-10, 12-35, 49 and 51-53 are pending.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 49 has been rejected as indefinite with respect to the term "filling." Applicants respectfully traverse the rejection for the following reasons.

The claim language at issue is "wherein the multivesicular liposomal particle composition is sterilized before filling." The Examiner has posed the question, "It is unclear what applicant intends to convey by 'sterilized before filling' in this claim. Where is it filled?" Applicants understand the Examiner's question to be alternatively expressed as "Into what is the composition filled?" The response is based on this interpretation of the rejection.

One of ordinary skill in the art, upon reading this language, with the understanding that pharmaceutical products are being produced, would immediately understand that the "filling" referred to in the claim, is filling of a package. For example, on page 5, lines 25-27 of applicants' written description, this is pointed out. Further information relevant to this question is disclosed in the paragraph bridging pages 11 and 12 of applicants' written description, in which sterilization of a filled container is compared to product sterilization before filling the container.

CERTIFICATE OF MAILING BY FIRST CLASS MAIL

I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, Washington, D.C. 20231.

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If the Examiner's question is to be taken more literally, reference is made to applicants' specification on page 12, line 18 to page 13, line 12. Applicants respectfully submit that the reference to sterilization "before filling" would be immediately clear to one of ordinary skill in the art. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Under 35 U.S.C. §103 Over Kim et al. (1987), Assil et al., Bonetti et al., Kim et al. '147 or Sankaram et al. in view of Lenk et al. (United States Patent No. 5,948,441)

Claims 1-10, 12-35, 49 and 51-53 have been rejected as obvious over Kim et al. (1987), Assil et al., Bonetti et al., Kim et al. '147 or Sankaram et al. in view of Lenk et al. Applicants respectfully traverse the rejection for the following reasons.

As the Office Action points out (page 3), none of Kim et al. (1987), Assil et al., Bonetti et al., Kim et al. '147 or Sankaram et al. disclose cross-flow (or tangential) filtration methods, nor do they disclose the making of a sterile preparation. The Office Action relies on Lenk et al. for disclosure of the cross-flow filtration method for size separation of particles to "select large quantities of a homogeneous, defined size distribution from a heterogeneously-sized population." (Office Action, page 3). Lenk et al. is also relied on for disclosure of the preparation of sterile solutions. (Office Action, page 4).

Lenk et al. discloses that tangential cross flow filtration is used to permit "large scale separation of ... particles into select size ranges, the size determined by the pore size of the filter employed" (col. 1, lines 17-19; emphasis added). Lenk et al. futher notes that the invention described therein "is directed towards the separation of particles according to size using the tangential flow filtration technique..." (col. 1, lines 46-48; emphasis added). As Lenk et al. points out, "[t]he control of particle size in a population is difficult and generally has not been successful." (col. 4, lines 12-13). Lenk et al. continues the discussion of prior art attempts to control the particle size in populations in col. 4, lines 21-64. Each of the methods noted involves either filtration or sonication/centrifugation to control particle size.

Lenk et al. discloses sizing of particles using "a first filter of first pore size between about 10 and about 0.2 μm..., which excludes particles above the defined cutoff, and a second filter of second pore size of between about 2000 molecular weight and 2 microns..." (col. 7, lines 56-60). Further description of the size ranges available are disclosed in Lenk et al. in column 8,

lines 35-55, in which it is specifically stated that "If a greater size is needed or acceptable, then, for example, a about 10 μm filter can be employed to obtain the upper cutoff." (col. 8, lines 53-55). Thus, it is clear that Lenk et al. is concerned with the separation of particle mixtures to obtain relatively homogeneous distributions of particles with sizes up to about 10 μm.

On the other hand, the claimed invention does not employ cross-flow filtration to obtain a "homogeneous, defined size distribution from a heterogeneously-sized population" as Lenk et al. teaches (col. 5, lines 2-3). The methods of the claimed invention produce compositions of homogeneous particle size, with highly stable particles, high encapsulation efficiency, and with high yield, without relying on cross-flow filtration to provide control over particle size.

As disclosed in applicants' specification, primary filtration (for example, diafiltration or cross-flow filtration) has several objectives: exchange of the second aqueous solution by an isotonic solution, concentration of the multivesicular lipid-based particles, and removal of unencapsulated drug. (page 25, lines 10-14). Cross-flow filtration is not used as a method of controlling the size distribution of particles produced according to the inventive method. In any case, cross-flow filtration using filters as described in Lenk et al. cannot be used to control the size distribution of particles of over 10 microns, since the pore sizes of those filters cannot achieve this objective.

According to the present invention, particle size distribution is controlled through control of the power input into the composition as the particles are being formed. For example, as disclosed in Example 2, control of the agitation speed results in particles within desirable particle size specification and with good particle size standard deviation. (page 36, line 1 to page 37 line 2, particularly page 36, lines 21-26). As a further example, as disclosed in Examples 6 and 8, there is an inverse relationship between power input and particle size for particles produced through the use of static mixers. (page 40, line 1 to page 45, line 2; page 45, line 17 to page 46, line 22; particularly page 44, lines 6-21, page 46, lines 13-19, and Figures 13, 14, and 15). There is no disclosure in applicants' specification of the use of any filtration step to further control the particle size or the particle size standard deviation.

In particular, with respect to claim 53, which requires that "the mean particle size before cross-flow filtration is within about 1 micron of the mean particle size after cross-flow filtration," Lenk et al. does not provide any teaching or motivation relevant to the claimed

invention. As disclosed in Lenk et al., particles initially having a size range of from 0.1 microns to 50 microns were cross-flow filtered to give particles between 1.2 and 5.0 microns (col. 8, lines 35-55). On the other hand, as disclosed in applicant's specification, the change in mean particle size upon cross-flow filtration according to the methods of the invention was negligible (Table 3, page 48, lines 15-22).

Clearly then, any teaching, suggestion, or motivation of Lenk et al. which relates to the use of cross-flow filtration in the production of particles can have no bearing on a process which uses power input into an emulsion to control particle size and distribution thereof. Without any suggestion or motivation to combine the cross-flow filtration of Lenk et al. with the other cited references, there is no *prima facie* case of obviousness based on the suggested combination. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection Under 35 U.S.C. §103(a) Over Kim et al. (1987), Assil et al., Bonetti et al., Kim et al. '147 or Sankaram et al. in view of Lenk et al. further in view of Kwasiborski et al. (United States Patent No. 6,033,708), Fenske et al. (United States Patent No. 5,837,282), Mehl Sr. et al. (United States Patent No. 5,885,260), Castor et al. (United States Patent No. 5,776,486) or Moynihan (United States Patent No. 5,589,189)

Claims 1-10, 12-35, 49, and 51-53 have been rejected as obvious over the references listed immediately above. Applicants respectfully traverse the rejection for the following reasons.

As set forth above, the instant claimed invention operates to produce particles of a specific size by control over the power input into the emulsification. The cited references do not teach this, and instead show the use of filters to control the size distribution of their particles.

Kwasiborski et al., for example, discloses the use of multiple passes through microfluidization apparatus to achieve their desired particle size distribution (see, for example, Tables 1-3 of Kwasiborski et al.). There is no suggestion that cross-flow filtration be used, in which the mean particle size is essentially unchanged (to within about a micron) through this step, as presently claimed.

Fenske et al. discloses the preparation of liposomes having encapsulated therapeutic compounds. The discussion in Fenske et al. regarding sizing of liposomes is found in col. 6, line

63 to col. 7, line 35. There is no discussion in Fenske et al. regarding cross flow filtration, and there is no suggestion found in Fenske et al. regarding the possible use of cross flow filtration. Applicants can find no teaching, or suggestion, that Fenske et al. discloses a method whereby the mean particle size of liposomes after cross-flow filtration would be within about a micron of the mean particle size before cross-flow filtration.

Mehl Sr. et al. discloses liposomes for delivery of therapeutic agents to the skin. Mehl Sr. et al. does disclose sterilization using 0.2 micron filters. Mehl Sr. et al. does not disclose or anywhere suggest the use of cross-flow filtration. This reference also does not disclose or suggest the limitation of claim 53, which requires that the cross-flow filtration result in a mean particle size change of about a micron or less.

Castor et al. discloses liposomes containing hydrophobic drugs. Castor et al. does not disclose the use of cross-flow filtration. Castor et al. does disclose sterilization using 0.2 micron filters. Castor et al. does not disclose or anywhere suggest the use of cross-flow filtration. This reference also does not disclose or suggest the limitation of claim 53, which requires that the cross-flow filtration result in a mean particle size change of about a micron or less.

Moynihan discloses liposomes sized by the application of a force (by a sonicator) which reduces the size of the liposomes (col. 3, line 66 to col. 4, line 5). Moynihan does not disclose or suggest the use of cross-flow filtration, and does not disclose the limitation of claim 53.

In summary, of the cited references, only Lenk et al. discloses cross-flow filtration. Lenk et al. teaches cross-flow filtration as "directed towards the separation of particles according to size using the tangential flow filtration technique..." (col. 1, lines 46-48; emphasis added). Lenk et al. does not employ cross-flow filtration such that "the mean particle size before cross-flow filtration is within about 1 micron of the mean particle size after cross-flow filtration," as required by the presently claimed invention. Applicants submit that there is no reference disclosing or suggesting the claimed aspects of the invention, and respectfully request reconsideration and withdrawal of the rejection on this ground.

CONCLUSION

Applicant asks that all claims be allowed. Enclosed is a $55 check for the Petition for Extension of Time fee. Please apply any other charges or credits to Deposit Account No. 06-1050, with reference to Attorney Docket No. 07333-043001.

Respectfully submitted,

Date: March 28, 2002

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